IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Christine A. Klein, *et al.*

Serial No.: 09/747,774

Filed: December 21, 2000

For: *METHODS AND COMPOSITIONS FOR IDENTIFYING RECEPTOR EFFECTORS*

Attorney Docket No.: 50370-60637C5DV

Group Art Unit: 1646

Examiner: Ruixiang Li

MS After Final
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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I hereby certify that this correspondence is being deposited with the United States Patent and Trademark Office by facsimile on the date indicated below.

Dated: September 14, 2005

Signature: Peter C. Lauro, Esq.

DECLARATION OF MARK POZNANSKY M.D., PH.D. UNDER 37 C.F.R. § 1.132

I declare as follows:

1. I, Mark C. Poznansky M.D., Ph.D., do hereby declare that I am an Assistant Professor of Medicine at the Harvard Medical School and AIDS Research Center of Massachusetts General Hospital. I am familiar with U.S. patent application No. 09/747,774 ("the present application"), and its prosecution. My experience and professional background are summarized in the attached curriculum vitae. I respectfully submit that I am qualified to speak and render opinions as to the disclosure in the present application and the state of the art.

2. I am compensated at a rate of $350.00 per hour in connection with my consideration of U.S. patent application No. 09/747,774 ("the present application") and its prosecution, and making this Declaration.

3. I am familiar with the Office Action mailed June 14, 2005 ("the Office Action"), issued by the United States Patent and Trademark Office in connection with the present application and make this Declaration in response thereto. I understand that the Office Action asserts that the instant invention lacks specific and substantial real world utility absent elucidation of the biological function of the orphan receptor and any role that the ligands identified as modulators of the receptor would play in modulation or identification of any disease state associated with that biological function. I also understand that the Office Action asserts that the biological function of orphan G-protein coupled receptors is "yet to be established."

4. The orphan receptors of the present invention are G protein-coupled receptors. The G protein-coupled receptors are structurally and functionally related proteins characterized by seven membrane-spanning alpha helices, an N-terminal segment on the exoplasmic face and a C-terminal segment on the cytosolic face of the plasma membrane. J. Darnell, *Molecular Cell Biology*, Chapter 17, pp. 656-657, 2nd edition (Scientific American Books, Inc., 1990). This large receptor family includes light-activated receptors (rhodopsins) in the eye and odorant receptors in the mammalian nose, as well as numerous receptors for various hormones and neurotransmitters. Although these receptors are activated by different ligands and may mediate different cellular responses, they all mediate a similar signaling pathway. J. Darnell, *Molecular Cell Biology*, Chapters 19-20, pp. 726-728 and 805-808, 2nd edition (Scientific American Books, Inc., 1990).

5. The signaling pathway of G protein-coupled receptors is well known in the art. The binding of ligands to the extracellular domain of G protein-coupled receptors induces a conformational change that allows the cytosolic domain of the receptor to bind to a G protein associated with the inner face of the plasma membrane. G proteins consist of

three subunits, designated α, β, and γ. This interaction activates the G protein, which then dissociates from the receptor and carries the signal to an intracellular target or "effector." Essentially, dissociation of the G-protein heterotrimer into G_α and $G_{\beta\gamma}$ units transmits the signal that the receptor has bound its ligand. J. Darnell, *Molecular Cell Biology*, Chapter 19, pp. 726-728, 2nd edition (Scientific American Books, Inc., 1990).

6. All G protein-coupled receptor ligand binding activates a G protein, which in turn activates or inhibits an effector that generates a specific second messenger or modulates an ion channel, causing a change in membrane potential. Adenylyl cyclase, which catalyzes the formation of cAMP from ATP, is the best-characterized effector regulated by trimeric G proteins. All adenylyl cyclase isoforms are stimulated by G_s, and certain isoforms are inhibited by G_i and $G_{\beta\gamma}$, G_s, G_i. As a result, adenylyl cyclase is stimulated or inhibited by many different G protein-coupled receptor ligands. J. Darnell, *Molecular Cell Biology*, Chapter 19, pp. 726-728, 2nd edition (Scientific American Books, Inc., 1990).

7. Once adenylyl cyclase catalyzes the formation of cAMP from ATP, the effects of cAMP are mediated through the action of cAMP-dependent protein kinases in all cells. J. Darnell, *Molecular Cell Biology*, Chapter 19, pp. 730, 2nd edition (Scientific American Books, Inc., 1990). The cAMP-dependent protein kinases phosphorylate substrate proteins, which in turn activate or inhibit enzyme systems to produce an appropriate hormonal response.

8. In addition to modulating adenylyl cyclase, activated G proteins trigger the activation of phospholipase C. Phospholipase C mediates the intracellular signaling pathway that produces the second messengers (e.g., Ca^{2+} and 1,2,diacylglycerol) responsible for the activation of protein kinase C. Protein kinase C isoforms in turn phosphorylate several cellular enzymes and receptors to produce an appropriate hormonal response. J. Darnell, *Molecular Cell Biology*, Chapter 19, pp. 741, 2nd edition (Scientific American Books, Inc., 1990).

9. I would not describe the biological function of orphan G-protein coupled receptors as "yet to be established," as all G protein-coupled receptors follow the same functional paradigm described above. To the contrary, the specific biological function of orphan G-protein coupled receptors is well established inasmuch as the biological function of G protein-coupled receptors, including orphan G-protein coupled receptors, enables ligands to modulate the intracellular activity of adenylyl cyclase and phospholipase C. Therefore, the orphan G-protein receptors described in the present application have a common, specific and well known biological function in cells.

10. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Dated 9/14/05

By:

Mark C. Poznansky M.D., Ph.D.,
Assistant Professor of Medicine at
the Harvard Medical School and
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